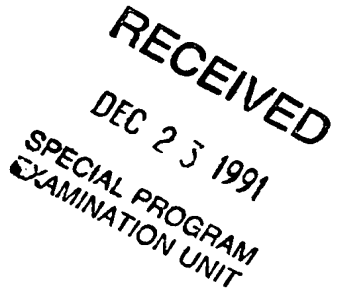
MR. Vanhoren

PATENT
PC7742JTL

#23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



IN RE:
U.S. PATENT NO. 4,517,359 :

ISSUED: MAY 14, 1985 :

TO: GABRIJELA KOBREHEL ET AL. :

FOR: 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYL-OXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF :

FROM: SERIAL NO. 304,481 :

OF: SEPTEMBER 22, 1981 :

Hon. Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. 156

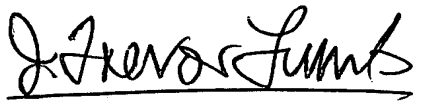
Transmitted herewith is the application of PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY for extension of the term of United States Patent No. 4,517,359 under 35 U.S.C. 156, together with a duplicate of the papers thereof, certified as such.

Please charge Deposit Account No. 16-1445 the amount of $1,000.00. The Commissioner is hereby authorized to charge any additional fees which may be

DS20093 01/08/92 4517359 16-1445 020 111 1,000.00CH

required, or credit any overpayment, to Deposit Account No. 16-1445. Two duplicates of this paper are enclosed.

Respectfully submitted,



Date: December 19, 1991

J. Trevor Lumb
Reg. No. 28,567
Tel.: (203) 441-4902

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340

PATENT
PC7742JTL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:
U.S. PATENT NO. 4,517,359 :

ISSUED: MAY 14, 1985 :

TO: GABRIJELA KOBREHEL ET AL. :

FOR: 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYL-OXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF :

FROM: SERIAL NO. 304,481 :

OF: SEPTEMBER 22, 1981 :

Hon. Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION
OF THE TERM OF UNITED STATES
PATENT NO. 4,517,359 UNDER 35 U.S.C. 156

Your applicant, PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY ("PLIVA"), an enterprise organized under the laws of Yugoslavia, and having its principal place of business at I. L. Ribara 89, 41001 Zagreb, Yugoslavia, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 4,517,359, granted to GABRIJELA KOBREHEL and SLOBODAN DJOKIC on the 14th day of May, 1985, for 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYLOXACYCLOPENTADECANE-2-ONE AND DERIVATIVES

THEREOF, by virtue of an assignment, recorded in the United States Patent and Trademark Office on the 22nd day of September, 1981, at Reel 3925, Frame 232. Pursuant to the provisions of 37 C.F.R. 1.730, your applicant hereby applies for an extension of the term of said United States patent of 1,267 days under 35 U.S.C. 156, based on the materials set forth herein and in the accompanying papers. In the materials which follow herein, paragraph numbers correspond to the paragraph numbers in 37 C.F.R. 1.740(a).

(1) The approved product is ZITHROMAX, which is further identified as follows.

Chemical Names

N-Methyl-11-aza-10-deoxo-10-dihydro erythromycin A

11-Methyl-11-aza-4-O-cladinosyl-6-O-desosaminyl-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyl-oxacyclopentadecane-2-one

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Generic Name

Azithromycin

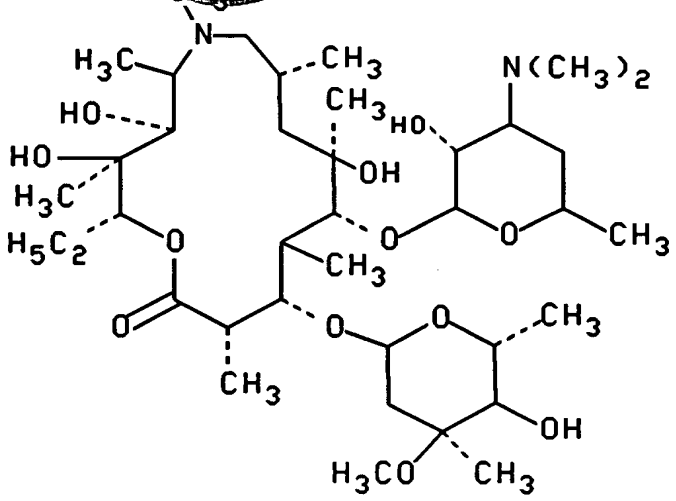
Molecular Formula

$C_{38}H_{72}N_2O_{12}$

Molecular Weight

780.5

Chemical Formula



(2) ZITHROMAX was subject to regulatory review under section 507 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 357).

(3) ZITHROMAX received permission for commercial marketing or use under section 507 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 357) on November 1, 1991.

(4) The active ingredient in ZITHROMAX is (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one (azithromycin). Said active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the

Public Health Service Act or the Virus-Serum-toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. 1.720(f). The last day on which this application could be submitted is December 31, 1991.

(6) The patent for which an extension is being sought is identified as follows.

Inventors: GABRIJELA KOBREHEL and SLOBODAN DJOKIC

Patent No.: 4,517,359

Title: 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYL-OXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF

Issued: May 14, 1985

Expires: May 14, 2002

(7) A copy of United States Patent No. 4,517,359, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) No disclaimer, certificate of correction or reexamination certificate has issued for United States Patent No. 4,517,359. A copy of the receipt of maintenance fee payment is attached hereto as EXHIBIT B.

(9) United States Patent No. 4,517,359 claims the approved product. Claim 1, the only claim in the patent, reads on the approved product. Claim 1 claims the chemical compound, N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A. The latter name is a chemical

name for azithromycin, the active ingredient of ZITHROMAX, the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows.

(a) An exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective for ZITHROMAX (azithromycin) on October 28, 1984, i.e., 30 days following receipt of Investigational New Drug ("IND") Application No. 24,999.

(b) A New Drug Application ("NDA") under section 507 of the Federal Food, Drug and Cosmetic Act for ZITHROMAX (azithromycin) was initially submitted on April 11, 1990, as NDA No. 50-670.

(c) NDA No. 50-670 was approved on November 1, 1991.

(11) A brief description of the significant activities undertaken by or for the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as EXHIBIT C.

(12) Applicant is of the opinion that United States Patent No. 4,517,359 is eligible for an extension under 35 U.S.C. 156, and the length of extension claimed is 1,267 days.

The requirements of 35 U.S.C. 156(a) and (c)(4) have been satisfied as follows.

(a) U.S. Patent No. 4,517,359 claims a product, ZITHROMAX (azithromycin).

(b) U.S. Patent No. 4,517,359 is currently set to expire on May 14, 2002 (i.e., the term of the patent has not yet expired).

(c) The term of U.S. Patent No. 4,517,359 has never been extended.

(d) This application for extension is being submitted by PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY, the owner of record of U.S. Patent No. 4,517,359, by its agent, in accordance with the requirements of 35 U.S.C. 156(d).

(e) The product, ZITHROMAX (azithromycin), has been subject to a regulatory review period under section 507 of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(f) No patent has to this date been extended, nor has any other extension been applied for, for the regulatory review period which forms the basis for this application for extension of the term of U.S. Patent No. 4,517,359.

The length of extension of the term of U.S. Patent No. 4,517,359 of 1,267 days claimed by applicant was determined according to the provisions of 37 C.F.R. 1.775 as follows.

(a) According to 37 C.F.R 1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate according to paragraphs (d)(1) through (d)(6) of 37 C.F.R. 1.775.

(b) According to 37 C.F.R. 1.775(c), the regulatory review period is the sum of (A) the number of days in the period beginning on the date on which the exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective and ending on the date the NDA was initially submitted under section 507 and (B) the number of days in the period beginning on the date the NDA was initially submitted and ending on the date the NDA was approved. The exemption under subsection 505(i) became effective on October 28, 1984, the NDA was initially submitted on April 11, 1990 and the NDA was

approved on November 1, 1991. Hence the regulatory review period is the sum of the periods from October 28, 1984 to April 11, 1990 and from April 12, 1990 to November 1, 1991. This is the sum of 1,991 days and 568 days, which is 2,559 days.

(c) According to 37 C.F.R. 1.775(d)(1)(i), the number of days in the regulatory review period which were on or before the date on which the patent issued must be subtracted. U.S. Patent No. 4,517,359 issued on May 14, 1985. Hence the period from October 28, 1984 to May 14, 1985 must be subtracted, leaving a reduced regulatory review period of from May 15, 1985 to April 11, 1990 and from April 12, 1990 to November 1, 1991. This is the sum of 1,793 days and 568 days, which is 2,361 days.

(d) 37 C.F.R. 1.775(d)(1)(ii) does not apply.

(e) According to 37 C.F.R. 1.775(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. 1.775(c)(1). This is one-half of 1,793 days, which is 896.5 days. After subtraction, and ignoring half days in the subtraction, this now leaves a reduced regulatory review period of 1,465 days.

(f) When the reduced regulatory review period of 1,465 days is added to the expiration date of U.S. Patent No. 4,517,359 (May 14, 2002), this gives a date of May 18, 2006. This latter date is later than November 1, 2005, the date obtained by adding 14 years to the date of approval of the approved product. Therefore, under paragraphs (d)(2) to (d)(4) of 37 C.F.R. 1.775, applicant is entitled to an extension corresponding to the period from May 14, 2002 to November 1, 2005. This is 1,267 days, which is the length of extension being claimed. Hence, applicant is in compliance with 35 U.S.C. 156(c)(3) and paragraphs (d)(2) to (d)(4) of 37 C.F.R. 1.775.

(g) The five-year limitation of 35 U.S.C. 156(g)(6)(A) and 37 C.F.R. 1.775(d)(5) applies to this application, because U.S. Patent No. 4,517,359 issued after the date of enactment of 35 U.S.C. 156. When 5 years is added to the expiration date of U.S. Patent No. 4,517,359 (May 14, 2002), this gives a date of May 14, 2007. The date obtained by adding the extension sought (1,267 days) to the expiration date of U.S. Patent No. 4,517,359 is November 1, 2005, which is

earlier than May 14, 2007. Hence, applicant is in compliance with 35 U.S.C. 156(g)(6)(A) and 37 C.F.R. 1.775(d)(5).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the 1,267-day extension being sought to the term of United States Patent No. 4,517,359.

(14) The prescribed fee for receiving and acting on this application for extension is to be charged to Deposit Account No. 16-1445, as authorized in the enclosed transmittal letter.

(15) Please address all inquires and correspondence relating to this application for patent term extension to:

J. Trevor Lumb
Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340

Tel.: (203) 441-4902

(16) A duplicate of these application papers, certified as such, is enclosed herewith.

(17) A declaration as set forth in 37 C.F.R. 1.740(a)(17) and 1.740(b) is enclosed herewith.

Respectfully submitted,

PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY

Date: December 19, 1991 by: J. Trevor Lumb

J. Trevor Lumb
Its Agent
Reg. No. 28,567
Tel.: (203) 441-4902

PFIZER INC
PATENT DEPARTMENT
EASTERN POINT ROAD
GROTON, CT 06340

EXHIBIT A

United States Patent [19]

Kobrehel et al.

[11] **Patent Number: 4,517,359**

[45] **Date of Patent: May 14, 1985**

[54] **11-METHYL-11-AZA-4-0-CLADINOSYL-6-0-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYL-OXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF**

[75] Inventors: **Gabrijela Kobrehel; Slobodan Djokic,** both of Zagreb, Yugoslavia

[73] Assignee: **Sour Pliva farmaceutska, kemijska prehrambena i kozmeticka industrija, n.sol.o.,** Zagreb, Yugoslavia

[21] Appl. No.: **304,481**

[22] Filed: **Sep. 22, 1981**

[30] **Foreign Application Priority Data**

Mar. 6, 1981 [YU] Yugoslavia 592/81

[51] **Int. Cl.**[3] **C07H 17/08**

[52] **U.S. Cl.** **536/7.4**

[58] **Field of Search** 536/9, 7.4

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,283,527	8/1981	Sciavolino	536/7.4
4,328,334	5/1982	Kobrehel et al.	536/7.4

Primary Examiner—Nicky Chan

Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57] **ABSTRACT**

11-Methyl-11-aza-4-0-cladinosyl-6-0-desosaminyl-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyl-oxacyclopentadecane-2-one and derivatives thereof, such as the 13,14-carbonate and C_1-C_3-alkanoyl derivatives thereof. The compounds exhibit antibacterial activity.

1 Claim, No Drawings

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

EXHIBIT B

PAYOR NUMBER
000586

POLLOCK, VANDE SANDE & PRIDDY
SUITE 800
1990 M STREET, N.W.
P.O. BOX 19088
WASHINGTON, DC 20036

RECEIVED
SEP 26 1988
POLLOCK, VANDE SANDE & PRIDDY

DATE MAILED
09/22/88

053471

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,519,886	173	450	----	06/573,732	05/28/85	01/25/84	04	NO	PAID
2	[redacted]	170	225	----	06/304,481	05/14/85	09/22/81	04	NO	PAID
3	4,511,442	173	450	----	06/609,536	04/16/85	05/15/84	04	NO	PAID
4	4,507,438	173	450	----	06/448,150	03/26/85	12/09/82	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	234
2	8A-157
3	171

EXHIBIT C

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY REVIEW PERIOD

DATE	ACTIVITY	COMMENTS*
09/26/84	Submission to FDA	IND-24,999 and Protocol 002 (Phase I, two-way single dose study with erythromycin). IND-24,999 became effective on 10/28/84.
06/10/85	Letter from FDA	Request for additional preclinical data; addressed issue of phospho-lipidosis.
10/16/85	Submission to FDA	Protocol 001 (assessment of prostatic and other male urological tissue concentrations). Reports for studies UK 202-002 and 201-002. Protocol 002 was cancelled.
10/28/85	Submission to FDA	Protocol 003 (assessment of tonsillar and adenoid tissue concentrations).
12/03/85	Submission to FDA	Annual Progress Report under 21 C.F.R. 312.33. Response to request of 06/10/85.
01/17/86	Submission to FDA	Protocol 006 (single-dose crossover study of safety and kinetics).
02/28/86	Submission to FDA	Protocol 004 (assessment of prostatic and other male urological tissue concentrations).
03/18/86	Submission to FDA	Protocol 006 modification.
03/19/86	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
03/25/86	Submission to FDA	Protocol 101 (multicenter for treatment of sexually transmitted diseases).
04/07/86 to 05/14/86	Protocol 101	First patient dose 04/07/86; last patient visit 05/14/86.
04/11/86 to 04/16/86	Telecons	Clinical hold established on Protocol 101.
04/29/86	Submission to FDA	Response to clinical hold on Protocol 101; modification of Protocol 101.
04/29/86	Submission to FDA	Protocol 007 (multiple dose safety and pharmacokinetics study).
05/22/86	Telecon	Discussion of Protocol 101 and clinical hold.

*For explanation of abbreviations, see last page.

DATE	ACTIVITY	COMMENTS
06/05/86	Submission to FDA	Protocol 001 modification.
06/16/86	Letter from FDA	Confirmed hold on clinical program; details of Protocol 101 deficiencies.
07/16/86	Submission to FDA	Protocol 003 modification.
08/20/86	Submission to FDA	Response to clinical hold on Phase II studies.
09/08/86 to 09/17/86	Telecons	Status of clinical hold discussed; meeting scheduled.
09/11/86	Submission to FDA	Protocol 004 modification.
09/17/86	Submission to FDA	Protocol 005 (assessment of gyneco-logical tissue and peritoneal fluid concentrations).
09/24/86 and 09/25/86	Telecons	Clinical hold on Protocol 101 only.
09/30/86	Submission to FDA	Additional investigators to Protocols 102, 103, 104; No hold on studies in URTI, LRTI, S & SST.
10/17/86 to 11/15/86	Protocol 102	First patient dose 10/17/86; last patient visit 11/15/86.
10/20/86 to 11/21/88	Protocol 103	First patient dose 10/20/86; last patient visit 11/21/88.
10/24/86 and 10/25/86	Telecons	Discussed clinical hold; meeting cancelled by FDA.
10/30/86	Submission to FDA	Protocol 007 modification.
11/18/86	Submission to FDA	Protocol 009 (bioavailability study).
11/19/86	Meeting with FDA	Discussion of status of clinical program and phospholipidosis
12/02/86	Submission to FDA	Protocol 005 modification.
12/01/86 and 12/12/86	Telecons	FDA agreed to one Phase II study with 20-30 patients; requested neuro-logical exams be done; other studies on hold; agreed to use of patients from URTI/LRTI/S&SST studies for neurological data.

DATE	ACTIVITY	COMMENTS
12/31/86	Submission to FDA	Response to 12/01/86 and 12/12/86 discussion; additional investigators to Protocols 102, 103 and 104.
01/12/87	Telecon	Studies may be initiated in S&SST,STD and LRTI studies with neurological examinations.
01/20/87	Submission to FDA	11/19/86 Division meeting minutes; Protocols 102, 103 and 104 modifications for review.
01/30/87	Submission to FDA	Additional investigators to Protocols 103 and 104.
02/09/87	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
02/17/87 to 11/02/88	Protocol 104	First patient dose 02/17/87; last patient visit 11/02/88.
02/19/87	Submission to FDA	Protocol 106 (comparative study for the assessment of safety and efficacy in LRTI).
02/24/87	Submission to FDA	Protocol 107A (dose-ranging comparative study in treatment of STDs).
02/26/87	Submission to FDA	Protocol 009 modification.
02/27/87	Submission to FDA	Concerning 01/12/87 telecon and neurological exams; Protocol 008 (comparison of neurological and audiometric safety).
03/18/87 to 11/11/87	Protocol 107A	First patient dose 03/18/87; last patient visit 11/11/87.
03/19/87	Submission to FDA	Annual Report under 21 C.F.R. 312.33.
03/20/87	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
03/23/87	Telecon	Discussed clinical studies.
04/17/87 to 06/21/88	Protocol 106	First patient dose 04/17/87; last patient visit 06/21/88.
04/23/87	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
05/21/87	Submission to FDA	Neurological examination data in response to telecon 01/12/87; request permission to include patients with pharyngitis and sinusitis.
05/21/87	Submission to FDA	Additional investigator to Protocol 104.

DATE	ACTIVITY	COMMENTS
05/22/87	Submission to FDA	Protocol 009 modification.
05/26/87	Submission to FDA	Protocol 003 modification.
05/29/87	Submission to FDA	Safety Report under 21 C.F.R 312.32.
06/04/87	Submission to FDA	Protocol 009 modification.
06/16/87	Submission to FDA	Results of neurological examination findings; plan to initiate Protocol 102 in 2-3 weeks.
06/26/87 and 06/29/87	Telecons	Clinical hold removed; request for more information concerning phospho-lipidosis issue.
06/30/87	Submission to FDA	Protocol 106 modification; additional investigators to Protocols 103 and 104.
07/30/87	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
07/31/87	Telecon	FDA comments on 06/16/87 clinical submission.
08/06/87	Submission to FDA	Protocol 010 (comparison of capsule to pediatric suspension).
08/17/87 and 08/18/87	Telecon	Discussed safety report.
08/25/87	Submission to FDA	Additional investigator to Protocol 102.
09/24/87	Submission to FDA	Protocol 107A modification.
10/21/87	Submission to FDA	Protocol 104 modification.
10/22/87	Submission to FDA	Summary of safety/efficacy data; request for End of Phase II meeting.
10/28/87 to 11/17/87	Telecons	Discussed end of Phase II meeting.
10/29/87	Submission to FDA	Response to 06/29/87 telecon re toxicology, phospholipidosis issues.

DATE	ACTIVITY	COMMENTS
11/12/87	Submission to FDA	Phase III clinical plan; Protocols for Division review: 108 (comparative study with Penicillin for treatment of streptococcal pharyngitis); 109 (comparative study with Ceclor for acute LRTI); 110 (comparative study with Keflex for S&SST); 111 (pilot study to determine the effect on Complobacter Pylori infections); 113 (comparative study with amoxicillin for acute sinusitis).
12/04/87	Meeting with FDA	End of Phase II Meeting, discussion of Phase III clinical plan.
12/10/87	Telecon	Phase III studies on clinical hold.
12/17/87	Telecon	Request for data on phospholipidosis in humans.
01/06/88	Telecon	Requested meeting with FDA.
01/06/88	Letter from FDA	Comments/requests concerning 01/16/85, 04/29/86, 08/20/86 submission re pharmacokinetic studies.
01/19/88	Telecon	Meeting with FDA scheduled.
01/20/88	Meeting with FDA	Discussed clinical hold.
02/01/88	Telecon	FDA requested outside expert reports on issues raised in clinical hold.
02/04/88	Meeting with FDA	Discussed pharmacologists' questions.
02/04/88	Submission to FDA	12/04/87 Meeting minutes; comments on clinical hold; proposed 02/24/88 meeting.
02/16/88 and 02/17/88	Telecons	Discussed planned preclinical studies, phospholipidosis issue.
02/24/88	Meeting with FDA	Discussed pharmacokinetic studies.
03/07/88	Submission to FDA	Protocol 102, 103, 104 and 003 modifications.
03/09/88	Meeting with FDA	Discussed status of consultants' review of animal safety data.
03/09/88	Submission to FDA	02/24/88 Meeting minutes.
03/23/88	Telecon	Discussed preclinical neonatal studies.
03/24/88	Submission to FDA	Protocol 114 (evaluation in treatment of STDs).

DATE	ACTIVITY	COMMENTS
03/24/88	Meeting with FDA	Received comments concerning 03/07/88 clinical submission.
03/31/88	Submission to FDA	Annual Report under 21 C.F.R. 312.33.
03/31/88	Letter from FDA	Pharmacology and clinical comments.
04/04/88 to 04/08/88	Telecons	Protocol 114 modification requested by FDA; discussed Advisory Committee Meeting and preclinical studies.
04/13/88	Telecon	Discussed 03/31/88 FDA letter.
04/27/88	Submission to FDA	Status report for 05/12/88 Advisory Committee Meeting.
05/03/88	Submission to FDA	Protocol 011 (determination of azithromycin in cerebrospinal fluid and assessment of peripheral blood lymphocytes for phospholipidosis).
05/03/88 and 05/04/88	Telecons	Discussed 04/27/88 submission.
05/09/88	Telecon	Discussed phospholipidosis.
05/12/88	Meeting with FDA	Advisory Committee Meeting closed session.
05/16/88 and 05/31/88	Telecons	Discussed Advisory Committee meeting.
06/01/88	Submission to FDA	Response to 03/31/88 FDA letter; Protocols 106, 108, 113, 109 and 110 modifications.
06/29/88	Submission to FDA	Safety Report under 21 C.F.R. 312.32.
07/13/88 to 07/28/88	Telecons	New medical officer; continued discussions on clinical hold and consultants' reports.
08/03/88	Submission to FDA	Protocol 015 (effect of concomitant antacid administration of absorption of azithromycin); Protocol 114 modification per Division request.
08/10/88	Submission to FDA	Response to clinical hold: expert reviews of preclinical.
08/10/88	Meeting with FDA	Response to clinical hold.
08/12/88	Submission to FDA	Additional preclinical information.
08/31/88	Telecon	Discussed Protocol 015.

DATE	ACTIVITY	COMMENTS
09/01/88	Submission to FDA	Proposed meeting agenda - phospholipidosis; proposed clinical studies; ophthalmological exams to be added to Protocols 108 and 109.
09/09/88	Telecon	Meeting arranged.
09/09/88	Submission to FDA	Preclinical reports in response to 01/20/88 meeting and 03/28/88 telecon.
09/19/88 to 09/22/88	Telecons	Clinical hold lifted; requested additional and modifications to preclinical studies.
09/23/88	Submission to FDA	Protocol 115 (treatment of early Lyme disease).
09/29/88	Telecon	Discussed 06/01/88 clinical submission.
10/07/88	Submission to FDA	Clinical program status; response to 09/19/88 telecon.
10/07/88	Submission to FDA	Revised preclinical study in response to 09/22/88 telecon.
10/07/88	Submission to FDA	Protocol 014 (assessment of gallbladder and hepatic tissues and bile for drug concentrations and phospholipidosis); Protocol 003 modification.
10/12/88	Submission to FDA	Protocol 016 (effect of concomitant cimetidine on the absorption).
10/25/88	Telecon	Advisory Committee Meeting scheduled for 11/17/88 cancelled by FDA.
10/25/88	Submission to FDA	Response to lifting of Phase III clinical hold; Protocols 108, 109, 110, 113 modifications.
10/27/88	Letter from FDA	Confirmation of removal of clinical hold on 09/19/88.
11/02/88	Letter from FDA	Comments re 08/10/88 submission on animal studies and outside consultant reports on phospholipidosis; ophthalmic examinations requested.
11/16/88 and 11/17/88	Telecons	Discussed ophthalmic examinations in response to FDA letter of 11/02/88.

DATE	ACTIVITY	COMMENTS
11/23/88 to 04/30/90	Protocol 108	First patient dose 11/23/88; last patient visit 04/30/90.
11/23/88 to 06/19/89	Protocol 119	First patient dose 11/23/88; last patient visit 06/19/89.
12/05/88 to 05/01/90	Protocol 109	First patient dose 12/05/88; last patient visit 05/01/90.
12/16/88	Submission to FDA	Re 02/24/88 meeting and 03/23/88 telecon; request permission to enter WCBP in clinical studies.
12/19/88 to 04/16/90	Protocol 110	First patient dose 12/19/88; last patient visit 04/16/90.
12/20/88	Submission to FDA	Additional investigators to Protocols 108, 109, 110 and 113.
12/22/88	Submission to FDA	Preclinical/clinical response to 11/02/88 FDA letter.
01/12/89	Submission to FDA	Protocol 017 (bioequivalency study comparing 250 mg tablet and 250 mg research capsule).
01/27/89	Submission to FDA	Additional investigators to Protocols 108, 109, 110, 113.
01/17/89 to 02/09/89	Telecon	WCBP may be entered into clinical studies.
02/27/89	Submission to FDA	Protocol 018 (bioequivalency study comparing reformulated cephalexin capsules vs. Keflex); Protocol 019 (comparing reformulated cefaclor capsules vs. Ceclor).
03/07/89	Submission to FDA	Protocols 108, 109, 110, 113 modified to allow WCBP. New Protocols: 116 (streptococcal pharyngitis); 117 (acute bacterial pneumonia); 118 (treatment of S&SSI).
03/22/89 to 04/30/90	Protocol 116	First patient dose 03/22/89; last patient visit 04/30/90.
03/27/89 to 04/13/90	Protocol 118	First patient dose 03/27/89; last patient visit 04/13/90.

DATE	ACTIVITY	COMMENTS
04/07/89 to 05/24/90	Protocol 117	First patient dose 04/07/89; last patient visit 05/24/90.
04/10/89	Submission to FDA	Annual Report under 21 C.F.R. 312.33.
04/12/89	Submission to FDA	Additional investigators for Protocols 116, 117, 118.
04/27/89	Submission to FDA	Protocol 115 modification; new Protocol 020 (bioequivalency comparing reformulated phenoxymethyl penicillin capsules vs. commercial tablets); additional investigators for Protocols 115, 108, 109, 110, 116, 117, 118.
05/18/89	Submission to FDA	Protocol 013 (assessment of pulmonary and other tissues for drug concentrations and phospholipidosis).
06/02/89	Submission to FDA	Additional investigators to Protocols 110, 115, 116, 117, 118.
06/12/89	Submission to FDA	Protocol 114X for treatment of STD.
07/06/89	Submission to FDA	Protocol 022 (bioequivalency study).
07/11/89	Submission to FDA	Protocols 108 and 109 addendum; additional investigators to Protocols 109, 115, 116, 117, 118.
08/17/89	Submission to FDA	Draft study report 104 for Division review; request for meeting.
08/31/89	Submission to FDA	Protocols 023, 024 and 025 (bioequivalency studies comparing tablets and capsules in various doses).
09/12/89	Submission to FDA	Protocol 014 modification.
09/29/89	Submission to FDA	Additional investigators to Protocols 109, 110, 113, 116, 117 and 118.
10/20/89	Meeting with FDA	Discussion of clinical study reports.
11/01/89 to 11/27/89	Telecons	Pre-NDA meeting scheduled for 01/04/90; discussed pediatric program submission to be filed mid-November.
11/09/89	Submission to FDA	Protocols 026 (effect of concomitant azithromycin on disposition of theophylline) and 125 (treatment of Chlamydia urethritis/cervicitis).

DATE	ACTIVITY	COMMENTS
11/17/89	Submission to FDA	Preclinical and clinical safety/efficacy summary; Protocol 126 (treatment of streptococcal pharyngitis in children).
11/21/89	Telecon	Discussed Chlamydia studies.
11/21/89 to 10/11/90	Protocol 125	First patient dose 11/21/89; last patient visit 10/11/90.
12/01/90	Telecon	Discussed status of review of pediatric submission of 11/17/89.
12/13/89	Submission to FDA	Confirm pre-NDA meeting.
12/18/89 and 12/19/89	Telecons	Discussed pediatric pharyngitis study.
12/28/89	Submission to FDA	Additional investigators to Protocols 109, 110, 113, 116, 117, 118 and 125.
01/04/90	Meeting with FDA	Pre-NDA meeting.
01/05/90 to 02/12/90	Telecons	Discussion of NDA format and content.
01/23/90	Telecon	FDA meeting scheduled for 02/12/90.
01/24/90	Submission to FDA	Protocol 124 (treatment of gonococcal urethritis/cervicitis).
01/29/90	Submission to FDA	Additional investigators for Protocols 108, 109, 110, 113, 116, 117, 118, 125 and 126.
02/09/90	Submission to FDA	Annual Report under 21 C.F.R. 312.33.
02/09/90	Submission to FDA	Clinical response to FDA comments of 01/06/88; meeting scheduled.
02/21/90	Meeting with FDA	Discussed 02/09/90 submission, biopharmaceutics issues for NDA, CANDAR format.
02/23/90	Submission to FDA	Protocol 120 (treatment of chancroid); additional investigators to Protocols 109, 124, 125 and 126.
03/12/90	Submission to FDA	Protocol 014 modification; additional investigators for Protocols 117, 120, 125 and 126.
03/26/90	Submission to FDA	Pilot Protocol 127 (treatment of Lyme disease).

DATE	ACTIVITY	COMMENTS
03/30/90 to 04/11/90	Telecons	CANDAR for Biopharmaceutics Division discussed.
04/05/90	Submission to FDA	Protocols 027 (bioequivalency study of reformulated amoxicillin capsule vs. commercial) and 123 (treatment of syphilis); additional investigators to Protocol 125.
04/11/90	Submission to FDA	NDA 50-670 submitted.
04/30/90	Letter from FDA	Acknowledged receipt of NDA.
05/02/90	Submission to FDA	Protocols 029, 030, 031 (bioequivalency studies).
05/18/90	Telecon	Discussed Protocol 128.
05/23/90 and 05/31/90	Telecon	NDA clinical question discussed.
05/24/90	Submission to FDA	Protocol 129 (treatment of early Lyme disease); preliminary results from Protocol 115.
05/29/90	Submission to FDA	Protocol 126 modification; additional investigators to Protocols 120 and 126.
05/31/90	Submission to FDA	Response to 05/23/90 telecon (pharyngitis studies).
06/05/90 and 06/06/90	Telecon	NDA microbiology question discussed.
06/05/90	Meeting with FDA	Preclinical and clinical data for NDA discussed.
06/13/90	Submission to FDA	Response to 06/05/90 meeting and 06/06/90 telecon.
06/14/90	Submission to FDA	Protocol 128 (pediatric study for otitis).
06/26/90	Facsimile from FDA	NDA clinical review comments.
06/28/90	Submission to FDA	Additional investigators to Protocols 125, 126 and 129.
06/28/90 to 07/06/90	Telecons	Clinical issues discussed.

DATE	ACTIVITY	COMMENTS
07/16/90	Submission to FDA	Protocol 130 (comparative trial in gonococcal urethritis/cervicitis).
07/19/90	Meeting with FDA	Clinical issues of NDA review discussed.
07/26/90	Submission to FDA	Protocol 125 modification; additional investigators to Protocols 120, 125, 127, 129 and 130.
07/27/90 and 08/02/90	Telecons	Discussions of NDA review.
07/30/90	Submission to FDA	Clinical responses sent by facsimile.
07/30/90	Telecon	FDA query (safety/efficacy 2 gm dose).
07/31/90	Telecon	Discussion of package insert; request for meeting.
08/02/90	Meeting with FDA	Discuss responses to FDA queries and status of clinical review of NDA.
08/03/90	Submission to FDA	Re 02/21/90 meeting and telecons of 04/11/90 and 08/02/90; NDA pharmacokinetics and bioavailability electronic data.
08/08/90	Submission to FDA	Responses to questions raised during Division NDA review.
08/07/90 and 08/15/90	Telecons	Clinical information requested for NDA.
08/09/90	Submission to FDA	Protocol 128 modification; safety data for Protocols 126 and 128; request approval to initiate Protocol 128.
08/10/90	Facsimile from FDA	Request for revised NDA efficacy tables.
08/10/90	Submission to FDA	Hard copy and disc of proposed package insert provided as requested in 08/07/90 telecon.
08/17/90	Submission to FDA	NDA clinical response to 08/07/90 telecon; two discs provided.
08/17/90	Letter from FDA	Acknowledged receipt of 07/30/90 NDA amendment; considered major amendment; new due date 01/29/91.

DATE	ACTIVITY	COMMENTS
08/21/90 to 08/31/90	Telecons	Discussion of NDA package insert.
08/28/90	Submission to FDA	Response to information requested in 08/15/90 telecon.
08/24/90 and 09/06/90	Telecons	Status of NDA pharmacology review and clinical issues discussed (Protocol 128); request for information on prothombin times.
09/07/90	Submission to FDA	Response to 07/30/90 telecon safety/efficacy 2 gm dose faxed on 07/31/90; additional investigators to Protocols 125, 129 and 130.
09/14/90	Submission to FDA	Confirmation of 09/26/90 meeting; Chlamydia amendment.
09/19/90	Telecon	Request for neonatal dog study; Protocol 130 modifications requested by FDA.
09/21/90	Submission to FDA	Methods validation and samples sent to validation lab.
09/25/90	Submission to FDA	Safety Update.
09/26/90	Submission to FDA	Clinical information in response to 07/30/90 and 07/31/90 telecons; interim reports for Protocols 114 and 124.
09/26/90	Meeting with FDA	NDA clinical issues and Chlamydia claim discussed.
09/26/90	Telecon	Package insert discussed.
10/02/90	Submission to FDA	Clinical information requested 08/10/90.
10/03/90 to 10/17/90	Telecons	Clinical information and manufacturing/stability information requested; Protocol 130 comments.
10/09/90 and 10/11/90	Telecons	Environmental Impact Analysis Report requested.
10/15/90	Submission to FDA	Annual Report under 21 C.F.R. 312.33.
10/16/90	Submission to FDA	Neonatal animal studies as requested in 09/19/90 telecon; response to request for clinical data/revised safety update tables.

DATE	ACTIVITY	COMMENTS
10/17/90 and 10/18/90	Submissions to FDA	New Protocol 135; amended Protocol 128; additional investigators to Protocols 135, 127 and 130.
10/23/90	Submission to FDA	Response to request of 10/05/90 for manufacturing/stability data.
10/24/90	Submission to FDA	Response to telecons; amended Protocol 130.
10/25/90	Submission to FDA	Response to requests for LRTI/pharyngitis/pneumonia tables.
10/29/90	Telecon	FDA comments on draft Protocol on neonatal study in dogs submitted 10/16/90.
10/30/90 to 11/12/90	Submissions to FDA	New Protocol 134, 126Z; additional investigators for Protocols 134, 014, 127 and 130.
11/12/90	Submission to FDA	Environmental Impact Analysis Report as requested.
11/14/90	Telecon	Additional clinical information requested for 10/25/90 submission.
11/16/90	Submission to FDA	Clinical information as requested in telecon 11/14/90.
11/28/90	Facsimile from FDA	NDA chemistry section review comments.
12/03/90 and 12/07/90	Submission to FDA	New Protocol 028; additional investigators for Protocols 130 and 134.
12/03/90 to 12/10/90	Telecons	Discussed status of NDA review; chemistry issues; clinical information requested; withdrew efficacy data for one study site.
12/12/90	Submission to FDA	NDA efficacy data; restated data tables.
12/14/90	Submission to FDA	Response to 12/06/90 request for clinical/safety data.
12/18/90	Submission to FDA	Response to comments concerning trade name.
12/19/90	Telecon	Discussed Chlamydia study.
12/21/90	Submission to FDA Meeting with FDA	NDA amendment for Chlamydia claim; revised text of labeling; response to request for safety data. Discussed submission.

DATE	ACTIVITY	COMMENTS
01/02/91 and 01/23/91	Submission to FDA	Additional investigators to Protocols 127, 135, 130 and 134.
01/14/91	Letter from FDA	Acknowledged receipt of 12/21/90 amendment; considered major amendment.
01/16/91	Facsimile from FDA Telecon	EA Report and microbiology review.
01/18/91	Facsimile from FDA Telecon	Additional clinical information requested for post-NDA patients; EA report comments.
01/22/91	Submission to FDA	Response to 11/28/90 chemistry review comments.
01/23/91	Submission to FDA	Response to request of 01/18/91 for additional clinical data.
02/04/91	Telecon	FDA inspections in Yugoslavia - Pliva.
02/11/91	Telecon	Discussed NDA safety summary tables.
02/13/91	Meeting with FDA	Discussed status of biopharm review.
02/15/91	Telecon	Additional NDA clinical information requested.
02/19/91	Submission to FDA	Response to request of 02/15/91 concerning Protocol 125.
02/20/91 and 02/21/91	Facsimile from FDA Telecon	Chemistry review comments.
02/21/91	Submission to FDA	New Protocol 136 to study serum concentrations in children with streptococcal pharyngitis; additional investigator to Protocol 134.
03/11/91 and 03/12/91	Telecons	Meeting scheduled for 03/15/91; discussed revision to package insert; Brooklyn and Puerto Rico manufacturing site inspections planned.
03/14/91	Submission to FDA	Response to telecon of 02/11/91 (side effect data).
03/15/91	Submission to FDA	Response to comments of 01/16/91 (additional microbiology information); revised package insert (hard-copy and disc).

DATE	ACTIVITY	COMMENTS
03/15/91	Meeting with FDA	Discussed package insert, Chlamydia claim, EA report.
03/18/91	Letter from FDA	Comments regarding EA Report.
03/20/91	Telecons	Additional chemistry information and reformatted EA report requested.
03/25/91	Letter from FDA	Acknowledge receipt of 03/15/91 amendment; considered major amendment.
03/25/91	Telecon	Meeting scheduled for 04/11/91 to respond to EA Report comments.
03/28/91 to 04/03/91	Telecons	Methods validation discussed.
04/01/91	Facsimile from FDA	FDA comments on Protocol 136.
04/05/91	Submission to FDA	New Protocol L-0155 (comparison with erythromycin in treatment of community acquired pneumonia).
04/08/91	Submission to FDA	Assay validation items provided on 04/01/91.
04/11/91	Meeting with FDA	EA Report discussed; agreement on test plan.
04/16/91	Submission to FDA	Response to 03/20/91 telecon (liner change on child resistant cap).
04/16/91	Submission to FDA	Draft Protocol 163 (comparison with penicillin V suspension in children with streptococcal pharyngitis).
04/11/91 to 04/18/91	Meeting with FDA Telecons	Discussed NDA Clinical and Statistical reviews and Pliva inspection.
04/18/91	Facsimile from FDA	Comments on NDA submission of 03/15/91 and chemistry issues.
04/25/91	Submission to FDA	NDA Response to 04/11/91 meeting and 03/18/91 comments - EA Report.
04/26/91	Submission to FDA	New Protocol 137 (treatment of Chlamydia urethritis/cervicitis using 500 mg and 250 mg single dose therapy); additional investigators to Protocols 127 and 129.

DATE	ACTIVITY	COMMENTS
04/26/91 to 05/01/91	Telecons Meeting with FDA	EA test Protocols approved with comments.
04/30/91	Telecon	Discussed NDA review and reclassification.
05/01/91 and 05/03/91	Meeting with FDA Telecon	Discussed biopharmaceutics review and status; CANDAR format.
05/10/91	Submission to FDA	Rationale for the reclassification of this NDA to an A-1 status.
05/13/91	Submission to FDA	Protocol 136 amendment per FDA request.
05/06/91 to 05/21/91	Telecons Facsimile to FDA	Discussed chemistry issues; Pliva facilities site inspection status; Brooklyn inspection; Puerto Rico manufacturing site approval.
05/17/91 to 05/24/91	Telecons	Division meeting scheduled for 06/05/91 to discuss NDA and labeling; discussed NDA reviews.
05/21/91	Submission to FDA	New protocol L-0173 (Chlamydia one-dose trial).
05/23/91	Telecon	Discussed meeting scheduled 06/05/91, approvable letter, clinical, chemistry and FONSI.
05/24/91	Submission to FDA	NDA Response to Division CMC comments of 04/29/91.
05/28/91	Submission to FDA	Additional investigators to Protocol L-0173.
06/03/91	Submission to FDA	Safety Update per FDA request of 05/21/91.
06/03/91 to 06/25/91	Telecons	Advisory Committee Meeting on 07/18/91; meeting with FDA scheduled for 06/26/91; package for Advisory Committee.
06/05/91	Submission to FDA	NDA interim data on environmental Protocols.
06/05/91 to 06/27/91	Submission to FDA	Additional investigators to Protocol L-0173.
06/11/91	Submission to FDA	NDA - Study Reports 110 and 118 per 06/06/91 FDA request.

DATE	ACTIVITY	COMMENTS
06/17/91	Submission to FDA	Updated Investigtors' Brochure; Protocols: 145 (amoxicillin and tetracycline as comparative agents) and 146 (erythromycin estolate and erythromycin base as comparative agents); additional investigators to Protocol 129; preclinical report.
06/26/91	Meeting with FDA	Discussion of issues for Advisory Committee Meeting; reviewed presentation.
06/26/91	Submission to FDA	Protocols: L-0152 (treatment of adult conjunctivitis) and L-0157 (respiratory infection).
06/27/91	Letter from FDA	Acknowledged receipt of 06/11/91 amendment; considered major amendment.
06/28/91	Submission to FDA	Response to Division request: Pediatric Safety Data (Protocol 126 & AZM/I/89001); revised Protocols 128 and 134 for Division review; preclinical final study report WEL 90-252.
07/03/91	Submission to FDA	Safety Update - Case Report Forms.
07/03/91 to 07/31/91	Submission to FDA	Additional Investigators to Protocol L-0173.
07/01/91 to 07/11/91	Telecons/Meetings	Discussed background package for Advisory Committee meeting; package delivered to FDA.
07/09/91	Submission to FDA	Information package for Advisory Committee Meeting 07/18/91.
07/08/91	Letter from FDA	Facsimile re 07/18/91 Advisory Committee Meeting (Synopsis of Clinical Efficacy).
07/09/91 and 07/15/91	Telecons	Discussed questions for Advisory Committee meeting.
07/17/91 and 07/22/91	Submission to FDA	Amended Protocol 137; additional investigators to Protocols 127 and L-0157.
07/18/91	Meeting with FDA	Advisory Committee Meeting.

DATE	ACTIVITY	COMMENTS
07/25/91 and 07/26/91	Telecons	Status of internal labeling meeting; reclassification to 1B.
07/25/91 and 07/26/91	Telecons	Discussion of additional drug for Lyme disease patient in Protocol 127.
08/01/91	Submission to FDA	Re: 04/25/91, 05/25/91 and 06/05/91 NDA Submissions (EA).
08/01/91 and 08/02/91	Meeting/Telecon	Additional data for the FONSI.
08/02/91	Submission to FDA	Corrected Safety Update; Case Report Forms.
08/06/91 to 08/16/91	Telecons	NDA plant inspection issues settled; NY District Office approval letter; labeling issues discussed; Puerto Rico site approved.
08/08/91 and 08/16/91	Telecons	Status of NDA review; issues discussed.
08/08/91 to 08/28/91	Submission to FDA	Additional investigators to Protocols L-0173, L-0157 and 127; Protocol L-155 modification.
08/15/91 to 08/26/91	Telecons	Status of review of modifications to lower age in Protocols 128 and 134 and of neonatal dog study.
08/22/91 to 08/26/91	Telecons	Discussed studies 109 and 117 to support pneumonia indication; FDA requested reformatted clinical information for study 109; study 117 accceptable.
08/30/91	Telecon	NDA review complete; FDA faxed draft copy of package insert; approvable letter forthcoming.
08/30/91	Submission to FDA	Clinical information previously sent by facsiile 8/21, 23 and 26 (minutes of 12/04/87 End-of-Phase II meeting and 1/4/90 Pre-NDA meeting, patent information, summary of efficacy data and patient information for Protocol 109).

DATE	ACTIVITY	COMMENTS
09/03/91	Letter from FDA	Approvable Letter: Request Draft Labeling; carton/container labeling; commitment to phase 4 studies; drug metabolism data; advertising copy.
09/04/91	Telecon	Discussed changes made to draft package insert; FDA meeting planned for 09/09/91.
09/04/91	Telecon	Discussed EA reports and biodegradation studies; final set of reports to be submitted.
09/06/91	Submission to FDA	Agenda and list of attendees for FDA meeting (09/09/91) for proposed Package Insert.
09/09/91	Submission to FDA	Protocol 034 (comparison of bioequivalency of 1000 mg sachets and 250 mg capsules).
09/09/91	Meeting with FDA	Discussed NDA Approvable Letter - Package Insert; data to support acute exacerbation of chronic bonchitis indication will be submitted.
09/10/91	Submission to FDA	EA Report.
09/11/91	Submission to FDA	Amendment planned in response to 09/03/91 NDA Approvable letter.
09/13/91 to 09/26/91	Submission to FDA	Additional investigators to Protocols L-0157, L-0173 and L0155.
09/13/91	Submission to FDA	Response to request at 09/09/91 NDA meeting; additional analysis of Protocol 109.
09/17/91 and 10/01/91	Telecons	Discussed submitting minutes of 09/09/91 meeting and information package on pneumonia with revised labeling.
09/19/91 and 09/20/91	Meetings with FDA	Discussed analysis and pooled data for pneumonia claim.
09/24/91	Telecon	Discussed amended Protocols 128 and 134 to lower age range; preclinical and clinical data.
09/26/91	Telecon	Discussed results of Internal Division meeting (09/25/91) on pneumonia indication for NDA.

DATE	ACTIVITY	COMMENTS
09/26/91	Submission to FDA	Final document in support of Environmental Assessment data.
09/30/91 and 10/02/91	Telecons	Discussed package insert.
10/03/91	Facsimile from FDA	Review comments on amendments for Protocols 137, L-0155, L-0173 and 165.
10/03/91 to 10/28/91	Submission to FDA	Additional investigators to Protocols L-0155, L-0157 and L-0173.
10/03/91	Submission to FDA	Annual Progress Report under 21 C.F.R. 312.33.
10/04/91	Submission to FDA	Revised Package Insert.
10/08/91	Telecon	FDA reviewers will meet on 10/11/91 to discuss review of pneumonia and acute exacerbation of chronic bronchitis.
10/15/91 and 10/16/91	Telecons	Dr. Bowen recommends approval of pneumonia and acute exacerbation of chronic bronchitis indications; final decision and labeling to be discussed at next meeting.
10/17/91	Submission to FDA	Annual Progress Report Addendum to report the death of two patients.
10/24/91	Telecon	Status of review and FONSI; FOIA report.
10/28/91	Submission to FDA	Request for Meeting with Division concerning pediatric studies; attendees and agenda.
11/01/91	Letter from FDA	Approval of NDA-50-670; package insert revisions.

CANDAR - Computer Assisted New Drug Application

EA - Environmental Assessment

FONSI - Finding of No Significant Impact (re Environmental Assessment)

LRTI - Lower Respiratory Tract Infection

S&SST - Skin and Skin Structure

STD - Sexually Transmitted Disease

URTI - Upper Respiratory Tract Infection

WCBP - Women of Child Bearing Potential

PATENT
PC7742JTL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:
U.S. PATENT NO. 4,517,359 :

ISSUED: MAY 14, 1985 :

TO: GABRIJELA KOBREHEL ET AL. :

FOR: 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYL-OXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF :

FROM: SERIAL NO. 304,481 :

OF: SEPTEMBER 22, 1981 :

Hon. Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

DECLARATION ACCOMPANYING
APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. 156

I, J. TREVOR LUMB, declare as follows.

1. I am a patent attorney. I am a member of the Bar of the State of New York and I am authorized to practice before the Patent and Trademark Office, Registration No. 28,567.

2. I am employed by PFIZER INC, a corporation of Delaware, having a place of business at 235 East 42nd Street, New York, NY 10017, and I have general authority from PFIZER INC to act on its behalf in patent matters.

3. By contract dated October 22, 1987, PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY ("PLIVA"), an enterprise organized under the laws of Yugoslavia, having its principal place of business at I. L. Ribara 89, 41001 Zagreb, Yugoslavia, and the owner of United States Patent No. 4,517,359, granted to PFIZER INC the right to file on behalf of and as agent for PLIVA an application for extension of the term of U.S. Patent No. 4,517,359 under 35 U.S.C. 156, based on the regulatory review period of ZITHROMAX (azithromycin) referred to in the application being submitted herewith.

4. Attached hereto as EXHIBIT 1 is a copy of a power of attorney, which authorizes me to prepare, sign and file in the Patent and Trademark Office, on behalf of and as agent for PLIVA, an application under 35 U.S.C. 156 for extension of the term of U.S. Patent No. 4,517,359, based on the regulatory review period of ZITHROMAX (azithromycin) referred to in the application being submitted herewith.

5. I have reviewed and I understand the contents of the application of PLIVA, dated December 19, 1991, which is being submitted herewith for extension of the term of United States Patent No. 4,517,359 under 35 U.S.C. 156 and 37 C.F.R. 1.730.

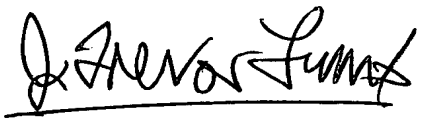
6. I believe that United States Patent No. 4,517,359 is subject to extension pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.710.

7. I believe that the length of extension of term of United States Patent No. 4,517,359 which is being claimed by PLIVA is justified under 35 U.S.C. 156 and the applicable regulations.

8. I believe that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 C.F.R. 1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application being submitted herewith or any extension of patent term granted thereon.

Signed this 19th day of December, 1991, at Groton, Connecticut.



J. Trevor Lumb
Reg. No. 28,567
Tel.: (203) 441-4902

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340

EXHIBIT 1

POWER OF ATTORNEY

PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY ("PLIVA"), an enterprise organized under the laws of Yugoslavia, and having its principal place of business a I.L. Ribara 89, 41001 Zagreb, Yugoslavia, represents: (1) that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 4,517,359 by virtue of an assignment, recorded in the United States Patent and Trademark Office at Frame 232, Reel 3925, on September 22, 1981; (2) that said patent discloses and claims the chemical substance described therein as N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A, known also as azithromycin; (3) that azithromycin is currently undergoing regulatory review by the United States Food and Drug Administration, before its commercial marketing or use; and (4) that by contract dated October 22, 1987, PLIVA granted to PFIZER INC ("PFIZER"), a corporation organized under the laws of Delaware, and having its principal place of business at 235 East 42nd Street, New York, New York, United States of America, an exclusive license under said patent, and the right to file on behalf of and as agent for PLIVA all applications, and to take all actions necessary, to obtain patent extension for said patent pursuant to the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, and any amendments thereof, based on said regulatory review of azithromycin;

and PLIVA now hereby appoints, authorizes and empowers the following named individuals:

PETER C. RICHARDSON, Reg. No. 27,526; MICHAEL J. PANTULIANO, Reg. No. 18,971; ALLEN J. SPIEGEL, Reg. No. 25,749; THOMAS C. NABER, Reg. No. 26,777; AARON PASSMAN, Reg. No. 26,787; GEZINA HOLTRUST, Reg. No. 28,222; J. TREVOR LUMB, Reg. No. 28,567; LAWRENCE C. AKERS, Reg. No. 28,587; RAYMOND W. AUGUSTIN, Reg. No. 28,588; JAMES M. MCMANUS, Reg. No. 28,642; PAUL H. GINSBURG, Reg. No. 28,718; MARK DRYER, Reg. No. 28,775; ELIZABETH O. SLADE, Reg. No. 29,011; JOHN L. LAPIERRE, Reg.

No. 29,185; GREGG C. BENSON, Reg. No. 30,997; A. DEAN OLSON, Reg. No. 31,185; ROBERT F. SHEYKA, Reg. No. 31,304; HOWARD R. JAEGER, Reg. No. 31,376; GROVER F. FULLER, JR., Reg. No. 31,760; MERVIN E. BROKKE, Reg. No. 32,723; KAREN DEBENEDICTIS, Reg. No. 32,977; VALERIE M. FEDOWICH, Reg. No. 33,688; and D. STUART MCFARLIN, Reg. No. 33,736;

all of whom are members of the PFIZER Patent Department and have general authority to act on behalf of PFIZER in patent matters, to prepare, sign and file in the United States Patent and Trademark Office, on the behalf of and as agent for PLIVA, an application under 35 U.S.C. 156 and 37 C.F.R. 1.730 and 1.740 for extension of the term of United States Patent No. 4,517,359, based on said regulatory review of azithromycin, and to take all actions and do all things with respect thereto and in support thereof, including the filing of requests for review under 37 C.F.R. 1.181, that PFIZER deems necessary and proper to obtain an extension of the term of United States Patent No. 4,517,359, based on said regulatory review of azithromycin, and to protect the rights of PLIVA and PFIZER.

Signed at Zagreb, Yugoslavia, on this 31st day of July, 1991.

PLIVA PHARMACEUTICAL, CHEMICAL, FOOD AND COSMETIC INDUSTRY

by: _____

Zdravko Tomičić, General Manager

In the presence of:

_____

Željko Bedeković, Director of Legal & Patent Office

(Typed or printed name of witness)